

REMARKS

I. Status of the claims

Claims 1-23, 28, 29, and 39-44 are pending in this application. Claims 3, 9, and 41-44 have been withdrawn by the Office for being directed to non-elected subject matter. No claim has been amended in this Response.

II. Rejections under 35 U.S.C. § 103 (a)

A. Claims 1, 2, 4-8, 22, 23, 28, 29 and 40

Claims 1, 2, 4-8, 22, 23, 28, 29 and 40 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 5,411,981 ("*Gaillard-Kelly*"), in view of U.S. Patent No. 4,946,870 ("*Partain*"), US Patent No. 5,658,559 ("*Smith*"), and Cremophor RH 40 Technical Information, 1997 ("Cremophor pamphlet"). Office Action at 3. Applicants respectfully traverse this rejection.

The Office alleges that *Gaillard-Kelly* "teaches that the phenylimidazolidines of instant formula (I) have anti-androgenic activity and are used in pharmaceutical compositions including creams, pomades, and lotions." *Id.* (citations omitted).

Moreover, the Office relies on *Gaillard-Kelly* for the following allegations:

- 1) According to the Office, the 4-[3-(4-hydroxybutyl)-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile compound recited in instant claim 4 is disclosed in Example 96 of *Gaillard-Kelly*. *Id.*
- 2) According to the Office, *Gaillard-Kelly* teaches "that the compositions are 'useful in dermatology' and can be used with other anti-acne components such as retinol or with a product stimulating the growth of hair such as Minoxidil (6-amino-4,4-piperidino-1, 2-dihydro-1-hydroxy-2-iminopyrimidine) for the treatment of alopecia." *Id.* The Office the cites instant claims 11, 12, and 23 but fails to explain the significance of the alleged disclosure in *Gaillard-Kelly* with respect to instant claims 11, 12, and 23; and

3) The Office argues that *Gaillard-Kelly* teaches adding a 5-alpha-reductase inhibitor to the composition, which in the Office's view "meets instant claims 16 and 17." *Id.* at 5.

With regard to *Partain*, the Office alleges that it "teaches a topical film-forming composition for delivering pharmaceutical actives with controlled release." *Id.* at 3. The Office further states that "[t]he reference teaches that the composition is useful as a delivery system for single or [a] combination of pharmaceutical active agents, including anti-acne agents (retinoic acid and benzoyl peroxide) and anti-alopecia agents (Minoxidil)." *Id.* The pharmaceutical active agents listed by the Office as being taught by *Partain* include "diazoxide, nifedipine and diltiazem; angiotensins (captopril)." *Id.* The Office also relies on *Partain* for its teaching that "chitosan derivatives are useful film formers and topically applied in the form of lotion, solution, cream, etc." *Id.* at 3-4. The Office further argues that *Partain* "provides the general teaching of using a film-forming agent as a controlled-release delivery system for anti-acne and anti-alopecia agents, either alone or in combination with other pharmaceutical agents." *Id.* at 4. The Office also relies on *Partain* for its alleged teaching of the use of solvents "such as ethanol or glycerin with the chitosan film forming agent." *Id.*

The Office relies on *Smith* because it allegedly "also teaches a film-forming lotion composition which forms [a] barrier on the surface of the skin to prevent evaporative loss of moisture from the skin, and protects the skin from environmental irritants." *Id.* The Office alleges that *Smith* teaches "polyquaternary polyvinylpyrrolidone such as polyquaternium-16 (polyvinylpyrrolidone/imidazolinium methocholride copolymers)" and then cites to instant claim 40, but fails to explain the significance of the *Smith* disclosure with respect to instant claim 40. *Id.* The Office also states that *Smith* discloses that

"[i]sopropanol is used as a solvent to dissolve pharmaceutical actives" and then cites to instant claim 8, but fails to explain the significance of the *Smith* disclosure with respect to instant claim 8. According to the Office, the pharmaceutical actives taught by *Smith* include the anti-acne actives, benzoyl peroxide and vitamin A.

Finally, the Office relies on the Cremophor pamphlet for its alleged teaching of polyoxyethylated (POE) hydrogenated castor oil, the elected plasticizer, which the Office acknowledges is not taught by *Gaillard-Kelly*, *Partain*, and *Smith*. *Id.* at 5. The Office points out that the Cremophor pamphlet "teaches that POE hydrogenated castor oil is skin compatible and solubilizes hydrophobic pharmaceuticals including vitamin A (retinoic acid)." *Id.* More specifically, the Office remarks that the Cremophor pamphlet teaches that "the [POE hydrogenated castor oil] product forms clear solutions in water and ethanol with fatty acids and fatty alcohols." *Id.*

The Office attempts to explain its rationale for why one of ordinary skill in the art would combine the foregoing references, by stating:

Partain and Smith would have obviously motivated one of ordinary skill in the art at the time the present invention to modify the teaching of Gaillard and formulate the active ingredients in a controlled-release composition because (a) Partain teaches that a film-forming composition "acts as a reservoir to continuously and uniformly deliver the actives as well as protect the tissue from further injury or insult, which negates the need for hair cover, and controls the dosage at a constant level; (b) Smith also teaches a film-forming formulation which provides controlled-release of the actives while protecting the skin and prevent loss of moisture of the skin.

Id. at 5.

In addition, the Office alleges that it would have been obvious to one of ordinary skill to "modify the composition of the combined references by adding POE

hydrogenated castor oil as motivated by Cremophor because (a) Smith, Gaillard, and Cremophor all teach using retinoic acid; and (b) Cremophor teaches that POE hydrogenated castor oil is a well-known solubilizer in pharmaceutical/cosmetic art, which solubilizes hydrophobic pharmaceutical agents to form a clear solution." *Id.* at 5-6.

Finally, the Office adds that "[t]he skilled artisan would have had a reasonable expectation of successfully producing a stable, clear cosmetic composition comprising retinoic acid and the compound of instant formula (I)." Office Action at 6.

In response, Applicants point out in the discussion below that claims 1, 2, 4-8, 22, 23, 28, 29 and 40 were nonobvious at the time of the invention in view of the cited art, at least because, i) the cited art, even when combined, fails to teach the addition of a plasticizer, which is an element of all the claims; and ii) the cited art fails to teach that compounds of formula (I) can be combined with the components recited in the instant composition and have the desired therapeutic effect.

1. The cited art fails to teach or suggest the addition of a plasticizer

Applicants respectfully submit that the Office has failed to make a *prima facie* case of obviousness because the Office has not explained how the combined disclosures of the cited references would have suggested all of the elements of the claims to one of ordinary skill in the art. For example, the Office has not explained how the cited art suggests the addition of a plasticizer to a composition having the rest of the elements of claim 1.

The Office alleges that the Cremophor pamphlet discloses POE hydrogenated castor oil, which is Applicants' elected plasticizer. However, Applicants respectfully point out that the Cremophor pamphlet fails to provide any teachings that Cremophor® RH 40, the commercial name for the POE hydrogenated castor oil disclosed by the Cremophor pamphlet, can be used as a plasticizer, as opposed to solubilizer. Additionally, even assuming, *arguendo*, that the Cremophor pamphlet would have suggested the use of Cremophor® RH 40 as a *solubilizer* for a composition that contained retinol, the Office has not explained whether such amounts of Cremophor® RH 40 when used as a solubilizer would have resulted in Cremophor® RH 40 functioning as a plasticizer (i.e., imparting "suppleness[]" and flexibility" to the composition). Specification at 9, lines 10-11. Thus, it would have been impossible for one of skill in the art at the time of the invention to have been able to look to the Cremophor pamphlet for teachings that support the addition of a plasticizer to a composition.

In addition, neither *Gaillard*, *Partain*, nor *Smith* contain any disclosure that would have suggested to one of ordinary skill in the art the addition of a plasticizer to a composition. As such, not only does the Cremophor pamphlet not provide teachings of a plasticizer, but there is no teaching among the remaining cited references that would have led a skilled artisan to understand that a plasticizer would have been desirable. Applicants respectfully remind the Office that claim 1 explicitly recites a plasticizer, and the Office has failed to indicate how the cited art would have suggested this limitation. Thus, Applicants submit that a *prima facie* case of obviousness has not been established, because all the elements of the rejected claims have not been suggested

by the cited art. Accordingly, at least for the foregoing reasons, Applicants respectfully request that the rejection under U.S.C. § 103 can be withdrawn

2. The cited art fails to suggest that compounds of formula (I) can be combined with the components of the claimed composition

Applicants respectfully point out that the Office has failed to articulate any reason why one of ordinary skill in the art after reading the cited references would have combined the compounds of *Gaillard Kelly* with the compounds of *Partain, Smith*, and the Cremophor pamphlet. The Office has failed to show that one of ordinary skill in the art would have had an expectation of success when combining the cited references to obtain a composition as instantly claimed.

Partain and *Smith* are completely silent as to the use of a plasticizer in their compositions, which are used to deliver active compounds to desired sites on a subject. Therefore, one of ordinary skill in the art would have had no expectation as to the impact of the use of a plasticizer in the compositions of *Partain* and *Smith*. Indeed, *Smith* teaches that "[t]he therapeutic agents should be chemically compatible with the other ingredients of the composition." *Smith* at col. 4, lines 47-48. The instant specification also explains that "precipitates of the substances at the application site after evaporation of the solvent" occurred with conventional aqueous/alcoholic hair lotions. Specification at p. 3, line 25 to p. 4, line 5. Therefore, even if the references were combined, the office has not provided any evidence that one of ordinary skill in the art would have expected that the compounds of *Gaillard-Kelly* would be chemically compatible with the ingredients of the compositions disclosed in *Partain* or *Smith*. The

Office seems to be advocating an "obvious to try" approach without providing the requisite expectation of success.

For example, in order to create a *prima facie* case of obviousness under an 'obvious to try' rationale, the U.S. Supreme Court in *KSR Int'l Co. v. TeleFlex Inc.* emphasized the need to articulate: 1) a finding that there was a recognized problem or need in the art, 2) a finding that there had been a finite number of identified, predictable solutions, 3) which would have given a person of ordinary skill a good reason to pursue the known options, and that in doing so the skilled artisan would **anticipate success**. M.P.E.P. 2143.E (citing *KSR*, 127 S.Ct. 1727, 1733 (2007)). Thus, under the M.P.E.P. and *KSR*, solutions that anticipate success must be present to establish a *prima facie* case of obviousness under an 'obvious to try' rationale. In this case, the Office has not met its burden because it has failed to explain how one of ordinary skill in the art would have expected to obtain a successful composition for the delivery of an active compound comprising, inter alia, a plasticizer, when no cited reference discloses a compound having such functionality.

The Office states that it would have been obvious to modify the composition of the claimed references "by adding to the composition POE hydrogenated castor oil as motivated by Cremophor because (a) Smith, Gaillard, and Cremophor all teach using retinoic acid; and (b) Cremophor teaches that POE hydrogenated castor oil is a well known solubilizer in pharmaceutical/cosmetic art, which solubilizes hydrophobic pharmaceutical agents to form a clear solution." Office Action at 5-6. The Office also adds that "[t]he skilled artisan would have had a reasonable expectation of successfully

producing a stable, clear cosmetic composition comprising retinoic acid and the compound of instant formula (I).” *Id.* at 6.

Applicants respectfully submit that the Office’s rationale of combining *Gaillard*, *Partain*, *Smith*, and the Cremophor pamphlet on the basis of using retinoic acid does not address the issue of whether or not it would have been desirable at the time of the invention to combine compounds of formula (I) with the other components of the claimed composition, such as a plasticizer. For example, there is no indication contained in the cited art that the compounds of formula (I) could be combined with a plasticizer, or even that such a combination would be desirable. Indeed, the cited references provided no teaching that indicated that POE hydrogenated castor oil could: i) be combined with compounds of formula (I); and ii) could be used as a plasticizer. Thus, the skilled artisan could not have known how POE hydrogenated castor oil would have affected the function and solubility of compounds of formula (I), based on the teachings of the cited art.

For example, with regard to the Office’s allegation that POE hydrogenated castor oil was a well-known solubilizer in the pharmaceutical cosmetic arts, Applicants emphasize that the Cremophor pamphlet explicitly states that “Cremophor RH 40 [a type of POE hydrogenated castor oil] is a solubilizer for fat-soluble vitamins, essential oils, and other hydrophobic pharmaceuticals.” Accordingly, Applicants point out that the compounds of formula (I) are not fat-soluble vitamins or essential oils, and that none of the cited references provided teachings that the compounds of *Gaillard Kelly* were among the hydrophobic pharmaceuticals that were soluble in POE hydrogenated castor oil. Thus, without teachings that the compounds of *Gaillard Kelly* could be classified as

among the limited number of pharmaceutical agents that are soluble in POE hydrogenated castor oil, it would have been impossible for a skilled artisan at the time **to have anticipated the success** of the composition resulting from the combined cited references in accordance with the requirements of the M.P.E.P. and *KSR*.

Thus, Applicants respectfully submit that the claimed invention is not obvious in view of the cited art for at least the reason that it would have been impossible for an ordinarily skilled artisan to have been able to anticipate the success of the claimed invention, as required by the M.P.E.P. and *KSR*. Accordingly, Applicants submit that the rejection of claims 1, 2, 4-8, 22, 23, 28, 29 and 40 under 35 U.S.C. 103(a) should be withdrawn.

B. Claim 15

The Office rejected claim 15 under 35 U.S.C. 103(a) as allegedly being unpatentable over *Gaillard-Kelly, Partain*, and the Cremophor pamphlet as applied to claims 1, 2, 4-8, 11-14, 16, 22, 23, 28, 29, and 40 above, and further in view of US Patent No. 5,541,220 ("*Ismail*"). Office Action at 6. Applicants respectfully traverse this rejection.

Claim 15 recites "[a] composition as claimed in claim 11, wherein at least one methylxanthine compound is chosen from pentoxifyllin, propentofyllin, and torbafyllin. The Office acknowledges that *Gaillard-Kelly, Partain*, and the Cremophor pamphlet fail to teach methylxanthine compounds. *Id.* The Office argues, however, that *Ismail* teaches agents for the treatment or protection of the skin and that *Ismail* exemplifies "a capsule that can treat alopecia, comprises pentoxifylin, vitamin E, and other

ingredients.” *Id.* The Office argues that it would have been obvious to one of ordinary skill in the art to add pentoxifylin to the composition of the combined references because *Ismail* and the references are directed to treating alopecia and *Ismail* teaches pentoxifyline as increasing blood circulation. The Office further argues that the skilled artisan would have been motivated to add pentoxifyline to the composition of the combined references because of the expectation of circulating the active agents of the composition through the body.

Claim 15 depends from claim 1 and would not have been obvious in light of the cited references, at least because the combined references fail to teach a composition comprising a plasticizer, fail to teach that compounds of formula (I) could be combined with the other components of the claimed composition, and fail to teach that POE hydrogenated castor oil is an appropriate solubilizer or plasticizer for compounds of formula (I). *Ismail* was cited only for its disclosure of pentoxifyline and fails to cure the deficiencies of the rest of the cited references. Therefore, because claim 15 incorporates the subject matter of claim 1, and claim 1 is not obvious over the cited art, claim 15 cannot be obvious in light of the cited references either. Accordingly, Applicants respectfully request that this rejection be withdrawn.

C. D. Claims 18 and 19

The Office rejected claims 18 and 19 under 35 U.S.C. 103(a) as allegedly being unpatentable over *Gaillard-Kelly*, *Partain*, *Smith*, and the Cremophor pamphlet as applied to claims 1, 2, 4-8, 11-14, 16, 22, 23, 28, 29, and 40 above, and further in view of EP 0427625 A (*Gaetani*). Office Action at 7.

Claim 18 recites “[a] composition as claimed in claim 11, wherein at least one hair growth-promoting compound is chosen from inner salts of 2,4-diamino-6-alkoxy-3-sulfoxypyrimidine hydroxide having from 1 to 6 carbon atoms in the alkoxy radical, pyridine 1-oxide compounds, and 2,6-diamino-1,3,5-triazine compounds.” *Id.* Claim 19 recites “[a] composition as claimed in claim 18, wherein at least one hair growth-promoting compound is an inner salt of 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide.” *Id.* The Office acknowledges that *Gaillard-Kelly* fails to teach 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide. *Id.* However, the Office argues that *Gaetani* “teaches internal salts of 2,4-diamino-6-alkoxy-3-sulfoxypyrimidine hydroxide for combating hair loss and inducing/stimulating hair growth.” *Id.* The Office further argues that it would have been obvious to one of ordinary skill in the art to add the 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide to the composition of the combined references because *Gaetani*, as well as *Gaillard*, are directed toward combating hair loss.

Applicants respectfully traverse this rejection. Claims 18 and 19 depend from claim 1, which would not have been obvious in light of the cited references at least because the combined references fail to teach a composition comprising a plasticizer, as explained above. *Gaetani* was cited only for its disclosure of 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide and fails to cure the deficiencies of the rest of the cited references. Therefore, because claims 18 and 19 incorporate the subject matter of claim 1, and claim 1 is not obvious over the cited references, claims 18 and 19 cannot be obvious in light of the cited references either. Accordingly, Applicants respectfully request that this rejection be withdrawn.

D. Claims 18 and 20

The Office rejected claims 18 and 20 under 35 U.S.C. 103(a) as allegedly being unpatentable over *Gaillard-Kelly, Partain, Smith*, and the Cremophor pamphlet as applied to claims 1, 2, 4-8, 11-14, 16, 22, 23, 28, 29, and 40 above, and further in view of WO 92/21317 (*Hocquaux*). Office Action at 8.

Claim 20 recites “[a] composition as claimed in claim 18, wherein at least one pyridine 1-oxide compound is 2,6-diamino-4-piperidinopyridine.” The Office acknowledges that *Gaillard-Kelly, Partain*, and the Cremophor pamphlet fail to teach 2,4-diamino-4-piperidinopyridine 1-oxide. *Id.* The Office argues, however, that *Hocquaux* teaches compositions containing a pyridine 1-oxide for combating hair loss and inducing/stimulating hair growth. *Id.* The Office further argues that the reference specifically discloses 2,4-diamino-4-piperidinopyridine 1-oxide. The Office argues that it would have been obvious to one of ordinary skill in the art to add the 2,4-diamino-4-piperidinopyridine 1-oxide to the composition of the combined references because *Hocquaux* and the other cited references are all directed toward combating hair loss.

Applicants respectfully traverse this rejection. Claims 18 and 20 depend from claim 1, which would not have been obvious in light of the cited references at least because the combined references fail to teach a composition comprising a plasticizer, as explained above. *Hocquaux* was cited only for its disclosure of pyridine 1-oxide compounds and fails to cure the deficiencies of the rest of the cited references. Therefore, because claims 18 and 20 incorporate the subject matter of claim 1, and claim 1 is not obvious over the cited references, claims 18 and 20 cannot be obvious in light of the cited references either.

For the foregoing reasons, the Office has not proved a *prima facie* case of obviousness in this rejection and Applicants respectfully request that the rejection be withdrawn.

E. Claims 18 and 21

The Office rejected claims 18 and 21 under 35 U.S.C. 103(a) as allegedly being unpatentable over *Gaillard-Kelly, Partain, Smith*, and the Cremophor pamphlet as applied to claims 1, 2, 4-8, 11-14, 16, 22, 23, 28, 29, and 40 above, and further in view of WO 91/19701 (*Hocquaux II*). Office Action at 8-9.

Claim 21 recites “[a] composition as claimed in claim 18, wherein at least one pyridine 1-oxide compound is 2,6-diamino-4-piperidinopyridine.” The Office admits that the combined references fail to teach 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide. *Id.* The Office argues, however, that *Hocquaux II* teaches compositions containing 2, 6-diamino-1,3,5-triazine derivatives for combating hair loss and inducing/stimulating hair growth and that 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide is disclosed in the examples. Office Action at 9.

The Office argues that it would have been obvious to one of ordinary skill in the art at the time the invention was made to add 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide to the composition of the combined references because all of the references are directed toward combating hair loss. *Id.*

Applicants respectfully traverse this rejection. Claims 18 and 21 depend from claim 1, which as explained *supra*, would not have been obvious in light of the cited references at least because the combined references fail to teach a composition

comprising a plasticizer. *Hocquaux II* was cited only for its disclosure of 2, 6-diamino-1,3,5-triazine derivatives and fails to cure the deficiencies of the rest of the cited references. Therefore, because claims 18 and 21 incorporate the subject matter of claim 1, and claim 1 is not obvious over the cited references, claims 18 and 19 cannot be obvious in light of the cited references either.

For the foregoing reasons, the Office has not proved a *prima facie* case of obviousness in this rejection and Applicants respectfully request that the rejection be withdrawn.

III. Conclusions

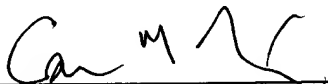
In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: July 31, 2008

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